

992,961



# PATENT SPECIFICATION

NO DRAWINGS

992,961

Date of Application and filing Complete Specification: July 28, 1961.  
No. 27512/61.

Application made in Switzerland (No. 8630) on July 28, 1960.

Application made in Switzerland (No. 7534) on June 27, 1961.

Complete Specification Published: May 26, 1965.

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Index at acceptance:—C2 C(2B18, 2B21, 2B40A, 2B40C, 2B40D, 2B40H1, 2B40H2, 2B40J1, 2B40J2, 2B40J3, 2B40J4, 2B40K, 2B40M, 2B50B1, 2B50B3, 2B50C1, 2B50C3, 2B50G1, 2B50G7, 2B53A2, 2B53C2, 2B53F, 2B53H1, 2B53H2, 2B53J1, 2B53J2, 2B53J3, 2B53J4, 2B53K, 2B53M, 2D6, 2D43B, 2D43C, 2D43D, 2D43E, 2D43F, 2D43G2, 2D43J)

Int. Cl.:—C 07 c, d

## COMPLETE SPECIFICATION

### Process for the manufacture of Amino Acid Derivatives

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with a new process for the manufacture of amino acid derivatives which are suitable for the synthesis of peptides, namely aminoacyl hydrazines and (of particular importance) N-acyl-N<sup>1</sup>-amino acyl hydrazines and their derivatives with protected functional (that is amino, hydroxy, mercapto or carboxyl) groups, and their acid addition salts. The term "aminoacyl" is used throughout this Specification to mean the acyl radicals of natural  $\alpha$ -amino carboxylic acids; "acyl" occurring as N-acyl throughout this Specification includes carboxylic, carbonic and sulphonic acid acyl groups.

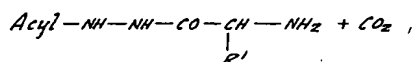
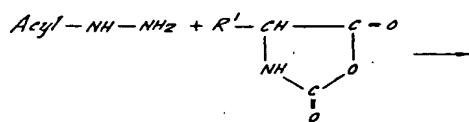
The N-acyl radical can also be an aminoacyl radical or an acylated amino acyl radical (including an amino-acylated aminoacyl radical, that is a peptide radical) or a protected amino-acyl radical.

The new compounds may be used as intermediate products in the synthesis of peptides. Particularly valuable are aminoacyl hydrazines which contain the tertiary butyloxycarbonyl radical as second acyl radical. These N<sup>1</sup>-aminoacyl-tertiary butylcarbazates are stable compounds which, according to Guttmann, couple with N-protected amino acid azides or peptide azides; they may also be used in the carbodiimide process or in the method of activated esters (for example paranitrophenyl ester). When used in the synthesis

of peptides it is advantageous that the tertiary butyloxycarbonyl group at the hydrazine may be simply and economically removed from amino-protected derivatives, for example N-carbobenzoxy derivatives, with the formation of amino-protected amino acid or peptide hydrazides which, in their turn, may be used for the azide-synthesis. Hydrazines which contain two aminoacyl radicals may be rearranged by a new process to form the corresponding peptide hydrazides in a simple manner and in excellent yield; the latter are valuable intermediate products in the synthesis of peptides.

According to the process of the present invention, the aforesaid aminoacyl - hydrazines or N - acyl - N<sup>1</sup> - aminoacyl - hydrazines are obtained by reacting a hydrazine or an N - acyl - hydrazine, respectively, with an  $\alpha$ -amino acid N-carboxyanhydride. The reaction is carried out under mild conditions. It is performed in the presence of a carboxylic acid, particularly an acid having a pK value of 3.7 to 5.7, for example propionic acid, butyric acid, benzoic acid, naphthoic acid, particularly acetic acid, and, if desired, in the presence of an inert organic solvent, such as dimethylformamide, chloroform, dioxan, tetrahydrofuran, ether or ethyl acetate, at room temperature; when the (solid) N-carboxyanhydride is added to the solution of the hydrazine or N - acyl - hydrazine, evolution of carbon dioxide occurs immediately, and the reaction has finished when the evolution of carbon dioxide ceases, which occurs after a short time, at most half an hour. When molecular quantities of the starting materials are used, the yield is quantitative. The reaction takes place, for example, according to the following equation:

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acyl representing the radical of an organic acid, such as that of an aliphatic, aromatic, araliphatic, heterocyclic acid, or a sulphonic acid or a carbonic acid monoester. Such acids are, for example, lower alkanic acids, such as formic acid, acetic acid, propionic acid, butyric acid or benzoic acid, phenylacetic acid, nicotinic acid, picolinic acid, benzenesulphonic acid, toluenesulphonic acid, amino acids or peptides, such, for example, as glycine, alanine, phenylalanine, proline, glutamine, glycyl-glycine, and especially carbonic acid mono-tertiary butyl ester. If acyl stands for an aminoacyl or peptide radical, free amino groups may be protected and also any other free functional groups, for example a hydroxyl, mercapto or carboxyl group. For the purpose of isolation the N - aminoacyl - N<sup>1</sup> - aminoacyl hydrazine may advantageously be converted first into an acid addition salt, for example the hydrochloride, hydrobromide or trifluoroacetate, by adding the acid in question to the solution. After the solvent has been evaporated, the salt of the N - acyl - N<sup>1</sup> - aminoacyl hydrazine is obtained in a yield of more than 90%. Resulting N - aminoacyl - N<sup>1</sup> - aminoacyl hydrazines may be rearranged to form the corresponding peptide hydrazides as described and claimed in our Specification No. 27513/61 [Serial No. 992,962]. In order to rearrange the N - aminoacyl - N<sup>1</sup> - aminoacyl - hydrazines it is necessary to use both an organic acid and an organic solvent in which the acid is dissolved. The rearrangement, as compared with the formation of the N - aminoacyl - N<sup>1</sup> - aminoacyl - hydrazines according to the process of the present invention, requires a much longer reaction time and a higher reaction temperature, for example about 8 to 20 hours at a temperature from 35 to 60° C.

The N - carboxyanhydrides may be prepared in a manner known *per se*, for example by reacting the amino acid with phosgene. During the reactions, functional groups which do not participate in the reaction, in particular the α-amino group of the amino acid hydrazide or peptide hydrazide, and, if required, also other amino, hydroxyl or mercapto groups present or a second carboxyl group, are advantageously protected in a known manner, particularly by means of radicals

which can be split off easily by hydrolysis, solvolysis or reduction, a free carboxyl or hydroxyl group, for example, by esterification or etherification, the mercapto group by the benzyl group, the amino group by the carbobenzoxy group, the tosyl group, the tertiary butyloxycarbonyl radical, the trifluoroacetyl radical or other acyl radicals known as protective groups. When the hydrazide of a peptide is used as starting material, it is also possible to employ the trityl radical with advantage.

From the resulting aminoacyl-hydrazines or N - acyl - N<sup>1</sup> - aminoacyl - hydrazines any protective groups present may be eliminated in a known manner by hydrolysis, solvolysis or reduction.

Depending on the method of working, the compounds are obtained in the form of bases or their acid addition salts. From the salts the bases may be obtained in a manner known *per se*. From the latter, salts can be obtained by reaction with acids which are suitable for forming therapeutically useful salts, such, for example, as salts with inorganic acids, such as hydrohalic acids, for example hydrochloric acid or hydrobromic acid, nitric acid, thiocyanic acid, sulphuric acid, phosphoric acid, or with organic acids, such as acetic acid, propionic acid, glycollic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, salicylic acid, 2 - phenoxy - benzoic acid, 2 - acetoxybenzoic acid, mandelic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, benzenesulphonic or toluenesulphonic acid.

The following Examples illustrate the invention:

#### EXAMPLE 1.

##### N - acetyl - N<sup>1</sup> - D:L - phenylalanylhydrazine

1.165 grams (15.7 millimols) of acetic hydrazide are dissolved in 30 cc of glacial acetic acid and 3.0 grams (15.7 millimols) of solid D:L - phenylalanine - carboxyanhydride are added to the stirred solution. When the evolution of carbon dioxide has subsided (after about 5 minutes) 2 cc of trifluoroacetic acid are added, the solution is evaporated at 40° C. at a water-jet vacuum and the oil remaining dissolved in 20 cc of chloroform. The trifluoroacetate crystallizes from the solution. After drying in a high vacuum (1 hour at 40° C.) there are obtained 5.03 grams of white crystals melting at 173—175° C. (94% of the theoretical yield).

By adding 17 cc of N - hydrochloric acid instead of trifluoroacetic acid and using the same method of working the hydrochloride is obtained. Beautiful little needles are obtained from methanol + ether which melt at 157—158° C. (with sintering).

1.675 grams (5 millimols) of the above

trifluoroacetate are suspended in 15 cc of ethyl acetate, and 0.70 cc (5 millimols) of triethylamine is added. On being shaken, all the substance dissolves and when left to stand overnight in a refrigerator at 0° C. N-acetyl-N<sup>1</sup>-D:L-phenylalanyl-hydrazine crystallizes in the form of beautiful crystals. After filtering and drying in a high vacuum there are obtained 970 mg (87.7% of the theory) melting at 140° C.

## EXAMPLE 2.

N - benzoyl - N<sup>1</sup> - D:L - phenylalanyl-hydrazine

500 mg (3.67 millimols) of benzhydrazide are dissolved in 10 cc of glacial acetic acid, and 702 mg (3.67 millimols) of solid phenylalanine - carboxyanhydride are added with stirring. Carbon dioxide evolves immediately which is suctioned off *in vacuo*. The solution is treated after 5 minutes with 0.5 cc of trifluoroacetic acid and evaporated at 40° C. at a water-jet vacuum. The oil remaining is dissolved in 20 cc of chloroform, filtered and a little petroleum ether is added. The trifluoroacetate crystallizes in the form of fine needles. The product is dried in a high vacuum for 1 hour at 40° C. to yield 1.39 grams (94.7% of the theory) of the trifluoroacetate melting at 175° C.

By adding N-hydrochloric acid instead of trifluoroacetic acid the hydrochloride melting at 218—219° C. (from methanol and ether) is obtained.

500 mg of the above trifluoroacetate are suspended in 5 cc of ethyl acetate, 0.18 cc of triethylamine is added and the mixture shaken, all the suspended substance dissolving. N - benzoyl - N<sup>1</sup> - D:L - phenylalanyl-hydrazine crystallizes slowly. After filtering and drying the product in a high vacuum, there are obtained 13.18 mg (90% of the theory) melting at 132° C. After recrystallization from petroleum ether the melting point remains at 132° C.

## EXAMPLE 3.

N - para - toluenesulphonyl - N<sup>1</sup> - D:L - phenylalanyl - hydrazine

931 mg (5 millimols) of tosylhydrazine are dissolved in 10 cc of glacial acetic acid, and 955 mg (5 millimols) of D:L - phenylalanine-carboxyanhydride are added with stirring. After 5 minutes, 5.5 cc of N - hydrochloric acid are added and the reaction mass evaporated at 40° C. at a water-jet vacuum. The residue is recrystallized from a mixture of methanol and ether to yield 1.76 grams (95% of the theory) of the hydrochloride melting at 224° C.

1.109 grams (3 millimols) of the above hydrochloride are dissolved with heating in 15 cc of water, 3 cc of N-sodium hydroxide solution are added, and the precipitated free base filtered off. After washing and drying in a desiccator over phosphorus pentoxide

there are obtained 920 mg (92% of the theory) of N - para - toluenesulphonyl - N<sup>1</sup>-D:L - phenylalanylhydrazine. Recrystallization from ethanol of 50% strength yields slabs melting at 116° C. with a transformation point of the crystals at 80° C.

## EXAMPLE 4.

N - tertiary butyloxycarbonyl - N<sup>1</sup> - D-leucyl - hydrazine

1.322 grams (10 millimols) of carbazinic acid tertiary butylester are dissolved at room temperature in 30 cc of glacial acetic acid and then treated with 1.572 grams (10 millimols) of D-leucine carboxyanhydride in one portion. The flask is attached to a water-jet vacuum until the evolution of gas ceases. After about 10 minutes, a little water is added and the solvent is removed at a water-jet vacuum at 35—40° C. The nearly colourless oil remaining is treated with absolute ether and, after a few hours, the crystals formed are filtered off. In order to remove the last traces of acetic acid, the reaction product is dissolved in a little water and agitated with a little weakly alkaline resin ("Amberlite IR-45"—Registered Trade Mark). After filtration, the reaction solution is evaporated at 40° C. under reduced pressure and the oil remaining treated with ether. The N-tertiary butyloxycarbonyl - N<sup>1</sup> - D - leucyl-hydrazine crystallizes out in the form of beautiful needles. Yield: 2.20 grams (90% of the theory). After recrystallization from a mixture of benzene and petroleum ether the product melts at 113—115° C.

In an analogous manner there may be obtained: N - tertiary butyloxycarbonyl-N<sup>1</sup> - glycyl - hydrazine melting at 143—146° C. (containing water of crystallization);

N - tertiary butyloxycarbonyl - N<sup>1</sup> - D:L-valyl - hydrazine, melting at 95—99° C. (. 1/2 H<sub>2</sub>O);

N - tertiary butyloxycarbonyl - N<sup>1</sup> - D:L-phenylalanyl - hydrazine, melting at 115—116° C. (. 1/2 H<sub>2</sub>O);

N - tertiary butyloxycarbonyl - N<sup>1</sup> - D-phenylalanyl - hydrazine melting at 111—112° C.;

N - tertiary butyloxycarbonyl - N<sup>1</sup> - L-prolyl - hydrazine melting at 94—104° C. (. 1/2 H<sub>2</sub>O).

## EXAMPLE 5.

N - carbobenzoxy - glycyl - N<sup>1</sup> - D - phenylalanyl - hydrazine

1.168 grams of carbobenzoxyglycine hydrazide are dissolved in 15 cc of glacial acetic acid and 1 gram of D - phenylalanine - N-carboxyanhydride is added. After 10 minutes, 1 cc of trifluoroacetic acid is added and the mixture is evaporated *in vacuo* at 40° C. The oil remaining is dissolved in 20 cc of chloroform. When the solution is allowed to stand, N - carbobenzoxyglycyl - N<sup>1</sup> - D - phenyl-

alanyl - hydrazine trifluoroacetate crystallizes out. The yield is 92%.

- 1.452 mg of trifluoroacetate are dissolved in 15 cc of water and 3 cc of N-sodium hydroxide solution are added dropwise. The precipitate formed is filtered off and dried under reduced pressure. 1.010 grams (91%) of N - carbobenzoxyglycyl - N<sup>1</sup> - D - phenylalanyl - hydrazine melting at 132° C. are obtained. After recrystallization from water, the log-shaped crystals melt at 135.5° C.

#### EXAMPLE 6.

N - carbobenzoxy - D - valyl - N<sup>1</sup> - D - valyl hydrazine

- 1.850 grams of carbobenzoxy - D - valine hydrazide are dissolved in 20 cc of glacial acetic acid and 1 gram of D - valine - N-carboxyanhydride is added. Carbon dioxide is evolved immediately. After 1/2 hour, hydrogen chloride is introduced and dilution is carried out with 40 cc of petroleum ether. The precipitate is filtered off and dried *in vacuo* over potassium hydroxide. 2.765 grams (98.7%) of the hydrochloride are obtained. After recrystallization from methanol/ether/petroleum ether (2:1:1), the N - carbobenzoxy - D - valyl - N<sup>1</sup> - D - valyl hydrazine hydrochloride melts at 206° C.
- 2.005 grams of hydrochloride are dissolved in 30 cc of water and 5 cc of 1-N. sodium hydroxide solution are added. A thick precipitate is produced which is filtered off, washed with water and dried *in vacuo* over phosphorus pentoxide. The yield is 1.72 grams (97%) F. = 218° C.

#### EXAMPLE 7.

N - benzoyl - glycyl - N<sup>1</sup> - D:L - phenylalanyl hydrazine

- 500 mg of hippuric acid hydrazide are dissolved in 10 cc of glacial acetic acid and 500 mg of phenylalanine - N - carboxyanhydride in solid form are added. Carbon dioxide is evolved immediately. After 5 minutes, 0.5 cc of trifluoroacetic acid is added and the solution is evaporated under reduced pressure at 40° C. The residue is crystallized from methanol/ether/petroleum ether (2:1:1). 1.175 Grams of N - benzoylglycyl - N<sup>1</sup> - D:L - phenylalanyl hydrazine trifluoroacetate having a melting point of 183—193° C. are obtained.

- 500 mg N - benzoylglycyl - N<sup>1</sup> - D:L - phenylalanyl hydrazine trifluoroacetate are suspended in 5 cc of ethyl acetate and 0.16 cc of triethylamine is added. The suspended substance is dissolved. After a short time, the N - benzoylglycyl - N<sup>1</sup> - D:L - phenylalanyl hydrazine crystallizes out (355 mg); m.p. 180° C.

- In the same way, starting from hippuric acid hydrazide and D - phenylalanine - N-carboxyanhydride, N - benzoylglycyl - N<sup>1</sup> - D - phenylalanyl - hydrazine having a melt-

ing point at 158° C.; optical rotation  $[\alpha]_{D^{20}} = -24.2^\circ$  (c=2 in methanol) is obtained; the trifluoroacetate melts at 175° C.

#### EXAMPLE 8.

N - L - Valyl - N<sup>1</sup> - L - valyl hydrazine

To a solution of 1 equivalent of hydrazine hydrate in 50 parts by weight of glacial acetic acid there are added 2 equivalents of valine-N-carboxyanhydride and the mixture is allowed to stand in a water-jet pump vacuum until the evolution of carbon dioxide has terminated.

#### EXAMPLE 9.

In an analogous manner to that described in Examples 5 and 6 and starting from N-benzoyl-glycine hydrazide and glycine-N-carboxyanhydride, N - benzoylglycyl - N<sup>1</sup> - glycyl - hydrazine, H<sub>2</sub>O melting at 173° C. (from water) is obtained; starting from N-benzoylglycine hydrazide and D - alanine-N - carboxyanhydride, N - benzoylglycyl - N<sup>1</sup> - D - alanyl - hydrazine trifluoroacetate melting at 191° C. is obtained; from N-benzoylglycylglycine hydrazide and D:L-phenylalanine - carboxyanhydride, N - benzoylglycylglycyl - N<sup>1</sup> - D:L - phenylalanyl-hydrazine, H<sub>2</sub>O melting at 208—212° C. is obtained; from N - carbobenzoxyglycine hydrazide and glycine - N - carboxyanhydride, N - carbobenzoxyglycyl - N<sup>1</sup> - glycyl-hydrazine, H<sub>2</sub>O melting at 146.5° C. (from water) is obtained; from N - carbobenzoxyglycine hydrazide and D:L - phenylalanine-carboxyanhydride, N - carbobenzoxyglycyl - N<sup>1</sup> - D:L - phenylalanyl - hydrazine melting at 152° C. is obtained; from N - carbobenzoxyglycine hydrazide and L - phenylalanine-carboxyanhydride, N - carbobenzoxyglycyl - N<sup>1</sup> - L - phenylalanyl - hydrazine melting at 135.5° C. is obtained; from N - carbobenzoxyglycine hydrazide and D - valine - carboxyanhydride, N - carbobenzoxyglycyl - N<sup>1</sup> - D - valyl - hydrazine melting at 131° C. is obtained; from N - carbobenzoxyglycine hydrazide and L - proline - carboxyanhydride, N - carbobenzoxyglycyl - N<sup>1</sup> - L - prolyl-hydrazine melting at 141—142° C. is obtained; from N - carbobenzoxyglycylglycine hydrazide and D:L - phenylalaninecarboxyanhydride, N - carbobenzoxyglycylglycyl - N<sup>1</sup> - D:L - phenylalanyl - hydrazine melting at 168° C. is obtained; from N - carbobenzoxyglycylglycine hydrazide and D - phenylalanine - carboxyanhydride, N - carbobenzoxyglycylglycyl - N<sup>1</sup> - D - phenylalanyl-hydrazine melting at 179—180° C. is obtained; from N - carbobenzoxy - L - valine hydrazide and glycinecarboxyanhydride, N-carbobenzoxy - L - valyl - N<sup>1</sup> - glycyl-hydrazine melting at 199—200° C. is obtained; from N - carbobenzoxy - L - valine hydrazide and O - acetyltyrosinecarboxyanhydride, N - carbobenzoxy - L - valyl - N<sup>1</sup> - (O - acetyl) - tyrosyl - hydrazine, C<sub>2</sub>H<sub>5</sub>OH

- melting at 187° C. (from ethanol of 50% strength) is obtained, from the latter by splitting off the acetyl group N - carbobenzoxy-L - valyl - N<sup>1</sup> - tyrosyl - hydrazine melting at 173—174° C. is obtained; from N - carbobenzoxy - L - phenylalanine hydrazide and D - valinecarboxyanhydride, N - carbobenzoxy - L - phenylalanyl - N<sup>1</sup> - D - valyl-hydrazine melting at 174—176° C. is obtained; from N - tosylglycine hydrazide and D - phenylalanine - carboxyanhydride, N-tosylglycyl - N<sup>1</sup> - D - phenylalanylhydrazine melting at 100.5° C. is obtained; from N-tosyl - L - proline hydrazide and D - phenylalanine carboxyanhydride, N - tosyl - L-prolyl - N<sup>1</sup> - D - phenylalanylhydrazine melting at 84° C. is obtained; from N - tosylglycine hydrazide and D - valinecarboxyanhydride, N - tosyl - glycyl - N<sup>1</sup> - D - valyl-hydrazine hydrochloride melting at 188° C. is obtained.

## EXAMPLE 10.

- N - para - nitrophenyl - N<sup>1</sup> - D,L - phenylalanyl - hydrazine hydrochloride
- 700 mg (4.75 mmols) of para-nitrophenyl hydrazine are dissolved in 15 ml of glacial acetic acid, and 873 mg (4.75 mmols) of solid D,L - phenylalanine - carboxylic acid anhydride stirred in. After 10 minutes, 4.7 ml of N-hydrochloric acid are added and the batch evaporated at 50° C. in a water-jet vacuum. The residual red oil is dissolved in methanol and the D,L - phenylalanyl - para-nitro - phenyl - hydrazine hydrochloride caused to crystallize by the addition of a 1:1 mixture of ether and petroleum ether. On drying over phosphorus pentachloride in a desiccator, 1.45 g (86% of theory) of chromatographically pure substance are obtained. This substance is recrystallized once more from the same solvents, and then melts at 234—236° C. (sublimation at 190° C.).
- In the same manner, the N - phenyl - N<sup>1</sup> - D,L - phenylalanyl - hydrazine hydrochloride of melting point 176—177° C. is obtained which sinters at 168° C.

## EXAMPLE 11.

- N - anilinoformyl - N<sup>1</sup> - D,L - phenylalanyl-hydrazine
- 756 mg (5 mmols) of 4 - phenylsemicarbazide are dissolved in 20 ml of glacial acetic acid, and 956 mg (5 mmols) of solid D,L-phenylalanyl - carboxylic acid anhydride stirred in. After 10 minutes, 5.5 ml of N-hydrochloric acid are added and the solvent expelled at 40° C. in a water-jet vacuum. The solid residue is crystallized from a mix-

ture of methanol and ether, and on drying 1.55 g (92.6% of the theory) of white crystals are obtained which melt at 196—198° C.

## WHAT WE CLAIM IS:—

1. A process for the manufacture of an aminoacylhydrazine or an N - acyl - N<sup>1</sup>-aminoacyl - hydrazine or a derivative thereof with a protected functional group (as hereinbefore defined) or an acid addition salt thereof, wherein a hydrazine or an N-acyl-hydrazine is reacted in the presence of a carboxylic acid, with an  $\alpha$ -amino acid - N - carboxyanhydride or a derivative thereof having a protected functional group.
2. A process as claimed in claim 1, wherein the reaction is carried out in the presence of a carboxylic acid having a pK value of 3.7 to 5.7.
3. A process as claimed in claim 1 or 2, wherein the reaction is carried out in the presence of glacial acetic acid.
4. A process as claimed in any one of claims 1 to 3, wherein the reaction is carried out in an organic solvent.
5. A process as claimed in claim 4, wherein the organic solvent is dioxan.
6. A process as claimed in any one of claims 1 to 5, wherein an N - aminoacyl - hydrazine is used as starting material.
7. A process as claimed in any one of claims 1 to 6, wherein tertiary butylcarbazate is used as starting material.
8. A process for the manufacture of an aminoacyl - hydrazine or an N - acyl - N<sup>1</sup>-aminoacyl - hydrazine or a derivative thereof with a protected functional group (as hereinbefore defined) or an acid addition salt thereof, conducted substantially as described in any one of the Examples herein.
9. An N - aminoacyl - N<sup>1</sup> - aminoacyl-hydrazine, or a derivative thereof having a protected functional group (as hereinbefore defined) or an acid addition salt of either compound.
10. An N - tertiary butyloxycarbonyl - N<sup>1</sup>-aminoacyl - hydrazine, or a derivative thereof having a protected functional group (as hereinbefore defined) or an acid addition salt of either compound.
11. Any one of the aminoacyl - hydrazines as claimed in claim 9 or 10 and described in the Examples herein.

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